Nature of the Non-traumatic Spinal Cord Injury Literature: A Systematic Review

Jillian M. Clark, PhD,¹⁻⁴ and Ruth Marshall, MBBS, DPRM, FAFRM (RACP)¹⁻⁴

¹South Australian Spinal Cord Injury Service, Hampstead Rehabilitation Centre, Lightview, South Australia, Australia;

²Spinal Injuries Unit, Department of Orthopaedics and Trauma, Royal Adelaide Hospital, Adelaide, South Australia, Australia;

³The University of Adelaide, Adelaide, South Australia, Australia; ⁴Centre for Orthopaedics and Trauma Research, University of Adelaide, South Australia, Australia

Background: Non-traumatic SCI (NTSCI) etiologies represent a markedly heterogeneous cluster of conditions defined within the consensus NTSCI taxonomy. This meta-analysis assembles evidence about the occurrence of NTSCI and its clinical outcomes with respect to 6 research domains. **Purpose:** To investigate the quality and quantity of clinical NTSCI evidence published in the peer reviewed literature with reference to prognosis, diagnosis, intervention, process of care, methodology, and qualitative approaches. **Methods:** PubMed and MEDLINE OVID MeSH heading searches were conducted for 5 common-language NTSCI descriptors. Filters were English language and Entrez date (1997-2016). Filters also controlled for case reports, editorials or errata, and invited reviews. NTSCI etiologies incorrectly classified, animal studies, and multidimensional mapping studies were excluded. Full texts were retrieved and ranked for evidence quality according to PRISMA statement guidelines, or PEDro criteria. Data were extracted and simple descriptive statistics applied. **Results:** The search terms non traumatic and non-traumatic SCI retrieved 282 articles, with 39 duplicates. After exclusion of 117 articles: Level 1V (60); NTSCI incorrectly evaluated (14); publication bias (2); non-English language (1); and animal experiments (1), 126 titles/abstracts were screened and ranked against criteria. Of the 8 papers allocated for full-text review, a subset of 3 articles was ranked level 1A (1) or level 11A (2); mean PEDro score 5.75±0.5. Reasons for full-text exclusions (5) were NTSCI incorrectly classified (1) and statistical limitations (4). Of the 6 domains, prognostics had adequate data yield (86) for evidence synthesis (4.8% ranked level 1A, or 11A). Notable evidence gaps were identified in qualitative (1), methodological (2), and diagnostic (8) domains. **Conclusion:** Therapeutic approaches require an evidence-based understanding of the distinct contexts in which NTSCI occurs, especially in less resourced settings. Our findings underscore the need for qualitative and quantitative research on the occurrence of NTSCI in all contexts. **Key words:** non-traumatic spinal cord injury, nontraumatic spinal cord injury, spinal cord disease, spinal cord lesion, systematic review

Our understanding of what constitutes non-traumatic spinal cord injury and how research evidence shapes this has been advanced considerably with the publication of a standardized taxonomy.¹ While pathophysiology has been a major research focus, the publication of a consensus position for the classification of non-traumatic etiologies allows for the possibility of a systematic approach to prognostics, diagnostics, and intervention through the framework of evidence-based medicine (EBM).² The mechanistic bases of a plethora of triggering events and initiating disease processes that contribute to the resultant neurological deficit across the spectrum of non-traumatic etiologies extensively have been investigated in animal models. The challenge is to interpret the epistemological strength of the clinical research evidence in accordance with the principles of EBM.²

Our understanding of the epidemiology of SCI largely has centered on trauma, as exemplified by the International Classification of External Causes of Injury (ICECI) World Health Organization Family of International Classifications (WHO-FIC).³ The multi-axial and hierarchical ICECI structure mirrors, to a large extent, that of the NTSCI standardized taxonomy.¹ The taxonomy was assembled after an iterative, consensus (Delphi) process to which over 100 key SCI experts contributed (researchers and clinicians, medical editors, and consumers). These advances are of fundamental importance to the logical next step in SCI population health – a systematic approach to the classification of the NTSCI literature.

In contrast to injury resulting from external causes,³ non-traumatic spinal cord dysfunction (SCD) is a consequence of multi-factorial and frequently complex disease processes.¹ Established

Corresponding author: Ruth Marshall, MD, Medical Director, South Australian Spinal Injury Service, Hampstead Rehabilitation Centre, 207 Hampstead Road, Northfield S.A., Australia 5085; e-mail: ruth.marshall@sa.gov.au

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preclinical models have revealed considerable complexity in the etiology of SCD associated with triggering events and initiating disease processes. This complexity introduces a need for a NTSCI medical evidence base that constrains bias² and optimizes knowledge translation.⁴ Although evidence synthesis to allow for the derivation of population-based guidelines for EBM was originated by Eddy,² it was subsequent work on population-level policies leading to the development of tools for the classification of research evidence, such as modified Sackett levels of evidence,⁵ the PRISMA statement,⁶⁻⁸ for reporting systematic reviews and meta-analyses of health care interventions (Prisma-statement.org; reviewed by Liberati et al⁷), and the Physiotherapy Evidence Base (PEDro) quality of trials score⁹ that marked a paradigm shift. A paradigm shift in NTSCI epidemiology, the development of a standardized non-traumatic taxonomy,¹ led us to investigate the nature of the NTSCI research evidence.

The broad goal of our systematic review of the NTSCI literature was to form a global hypothesis about the quality and quantity of the research evidence with respect to its scope and to explore systematic limitations for evidence synthesis and knowledge translation.⁴ Where evidence synthesis had occurred,¹⁰⁻¹³ our study aimed to elucidate the capacity of this experimental evidence base to inform health care standards and guide health policy. Our decision to perform a structured systematic review rather than a literature review was guided by the principle that population-based datasets can guide the care of an individual and can do so in tandem with policy. The specific goals of our study were to perform a systematic review of the non-traumatic research evidence in relation to English language articles published over 2 decades in peer-reviewed journals. Regarding research questions, we sought to clarify 2 issues across 6 investigative domains: in what way does the quality of the published research influence the scope for its synthesis, and how might research quality and quantity interact to shape this. For the purposes of our study, NTSCI was defined as the occurrence of a neurological deficit involving the spinal cord parenchyma, cauda equina, or conus medullaris that did not result from an external cause (reviewed by New and Delafosse¹⁴). In relation to the quality

of the retrieved articles, level 1A and 1B evidence were defined as “evidence from meta-analysis or randomised control trials” and “evidence from at least one randomised controlled trial,” respectively (modified Sackett Scale⁵; see **Appendix 1**).

Despite identification of a large literature, level 1A or 1B evidence was found for just 2 investigative domains (prognostics and interventions). There is good quality level 1A evidence for survival estimates reported in terms of standard mortality rates (includes 5 NTSCI datasets).¹⁰ Aspects of systematic bias involved the currency and geographic region of origin of the datasets available for synthesis.¹¹⁻¹³ Questions about interaction between the standardized NTSCI taxonomy and currency, as well as the integration of evidence bases derived from well-resourced and less well-resourced countries, warrant closer attention.

Methods

Selection

Original articles, systemic reviews, and meta-analyses reporting NTSCI in English language publications (January 1, 1997 to December 31, 2016) were included in this study (**Appendix 1**). The terms “nontraumatic spinal cord injury” [NTSCI], “non-traumatic spinal cord injury” [NT-SCI], “spinal cord lesion” [SCL], “spinal cord lesions” [SCLs], “spinal cord disease” [SCD], and “spinal cord injury not due to trauma” were selected after consultation with our facility’s research librarian. Terms were entered as the MeSH major topics with active language (English) and Entrez date (01/01/1997 – 31/12/2016) filters. Searches were performed in PubMed (NIH/OVID) and MEDLINE (OVID) databases, again after consultation with our research librarian; the latter repository offered the advantage of the “mp. search as Keyword” function (**Appendix 1**). Articles then were retrieved for each MeSH major topic term. Futility was set at 0 or greater than 1,000 retrieved articles per major MeSH topic term. An additional filter for publication type, using the term “case report,” “case studies” and then “review paper,” and “review” was added to the MeSH for each topic term that satisfied feasibility. Ineligible papers were extracted and each eligible

MeSH major topic term database was then checked manually for duplicates, including true duplicates, and duplicates contributing to publication bias [nonpublication of full studies, as defined by Moher et al^{8(p15)}] and ineligible articles (see **Appendix 1**: evidence quality ranked level 111 or 1V using the modified Sackett schema⁵). Case reports/series or pilot studies (each <10 subjects), errata, editorials, and review papers (with the exceptions of systematic reviews and meta-analyses) and study protocols were excluded from this analysis (as were reports in which SCI arising from external or nonexternal causes was incorrectly evaluated, eg, aortic aneurysm/iatrogenic SCI [TSCI]¹ or Surfer's myelopathy [NTSCI]).¹ Preclinical studies (eg, animal studies) were excluded as were multidimensional mapping studies.

Primary outcome measures were the quality and quantity of retrieved articles for the MeSH major topics "nontraumatic spinal cord injury" [NTSCI], "non-traumatic spinal cord injury" [NT-SCI], and "spinal cord lesion" [SCL] singular and plural; with retrieved articles for "spinal cord dysfunction" [SCD] and "spinal cord injury not due to trauma" designated as the secondary and tertiary outcome variables, respectively.

The final dataset for the primary outcome was compiled by pooling retrieved articles. Duplicate articles, if any, were extracted, as were ineligible studies. Data then were tabulated.

Ranking of data quality: PRISMA statement

Data were aggregated by author, year of publication, geographic region of origin, study methodology, Cochrane domain (prognosis, intervention, diagnostic, process of care,

methodological, and qualitative), and sample size (*n*) and were aggregated as NTSCI and SCD, and SCD alone. Each eligible article was ranked using the examiner-administered National Guideline Clearinghouse Evidence Based Health Care Practice Guidelines.⁵ This comprises a 6-scale schema that ranks evidence (see **Appendix; Table 1** extracted from ref. 5) according to levels of evidence (1-1V) and grades of recommendations (A-D)⁵; full texts were obtained for each eligible paper ranked 1A, 1B, or 11A. The methodological quality of the systematic review subset was gauged using PRISMA statement⁶ tools for the quality of reporting of systematic reviews and meta-analyses. The PRISMA statement consists of a 27-item checklist, 4-phase flow diagram (identification, screening, eligibility, and included phases) and table examples.⁷

Physiotherapy Evidence Base (PEDro)

The examiner-administered PEDro assessed evidence quality for the randomized controlled trial (RCT) subset.^{7,14} This 11-criteria scale dichotomizes each criterion into 1 of 2 categories ("satisfies" or "does not satisfy"), with a maximum summed score of 11. A PEDro quality rating of greater than 6 on the yes/no checklist was taken as the cut-off point for satisfactory evidence quality in an RCT. Evidence quality was ranked by 2 investigators (R.M., J.C.) who were blinded. Data then were pooled and final scores were reported as an average.

Statistical methods

Simple descriptive statistics were applied to nonparametric data (counts, percentages). Dichotomous data were converted to numeric

Table 1. Six-scale levels of evidence⁵

Levels of evidence	
1A	Evidence from meta-analysis or randomized control trials
1B	Evidence from at least one randomized controlled trial
11A	Evidence from at least one randomized controlled trial without randomization
11B	Evidence from at least one other quasi-experimental study
111	Evidence from nonexperimental descriptive studies, such as comparative studies
1V	Evidence from expert committee reports, or opinions, or clinical experience of respected authorities, or both

Data for this table were extracted from Schekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. *West J Med.* 1999;170(6):348-351.

variables, and binomial tests were applied. Parametric data were tabulated and descriptive statistics were applied. Data are reported as means and standard deviation of the means (*SD*). Statistical analysis was performed using IBM Statistical Package for Social Scientists (SPSS) Statistics and base 23 software.

Results

MeSH term “nontraumatic SCI”

A PubMed MeSH major topic search for “nontraumatic SCI” with filters (January 1, 1997 to December 31, 2016; English language) yielded 76 papers (**Figure 1**; search strategy, **Appendix 1**). Addition of a “case report” filter identified 4

Figure 1. Article retrieval flow diagram.

articles, yielding 72 eligible articles. Addition of a “review” filter retrieved 13 articles. Of these, 3 were duplications (each was a case report and excluded). An abstract screen conducted on the 76-article dataset identified 31 ineligible articles. Excluded articles comprised case reports (14), review papers (8), protocol (1), fragmented paper (1), animal study (1), and NTSCI incorrectly evaluated,¹ that is, either SCI evaluated as TSCI or TSCI evaluated as NTSCI (6). Of these 6 articles, 2 were surgical laminoplasty reports and 1 was a report of Surfer’s myelopathy (NTSCI incorrectly evaluated). This interim dataset consisted of 46 original papers, of which 2 were RCTs (level 1B) from the same group^{15,16} and 1 was a systematic review.¹² Substantial overlap was evident between the methodologies of Esclarín-Ruz et al¹⁵ and an earlier RCT co-authored by Esclarín-Ruz.¹⁶ The co-authored article¹⁶ was retrieved; was categorized as a duplicate, which could contribute to publication bias; and was excluded. Thirty-one (41%) of articles with the MeSH term “nontraumatic” were excluded. The final nontraumatic sample consisted of 45 retrieved articles.

MeSH term “non-traumatic spinal cord injury”

Search MeSH term “non-traumatic spinal cord injury” with the above-listed filters retrieved 103 articles (**Figure 1**). The addition of the publication type filter with the term “case report” retrieved no articles, contrasting with the results (4) for NTSCI using the same filter. In contrast to the systematic PubMed filter audit, manual audit of retrieved titles/abstracts identified 38 ineligible articles (case reports [18], reviews [13], fragmented papers [2], NTSCI incorrectly evaluated [3], each categorized as surgical trauma, animal studies [1], and an editorial [1]). Sixty-five retrieved articles were deemed eligible and screened. None of the eligible articles was a duplicate. Of these, 3 were systematic reviews (level 1A) and 2 were RCTs (level 1B).

OVID Mp. search as keyword function

In contrast to the quantity of the data obtained with PubMed, the corresponding MEDLINE (OVID) database searches with a “mp. search

as Keyword” function retrieved 64 articles: 30 nontraumatic and 34 non-traumatic (**Figure 1**). Of these, 16 were deemed eligible. Thirty-nine were duplicates and the remainder were ineligible (5 NTSCI incorrectly evaluated as TSCI; 1 non-English language, and 3 level 1V evidence).

The results (**Figure 1**) obtained for the primary outcome measures (243 retrieved articles) contrasted markedly with the 53,117 (3,823 in 2016 alone) and 79,182 PubMed articles retrieved using the Major MeSH topics “spinal cord disease” and “spinal cord injury not due to trauma,” respectively. Because retrieval rates less than 10 or greater than 1,000 satisfied cut-off points for futility, no further analysis was conducted.

MeSH term “spinal cord lesion”

Despite the retrieval of 76 and 103 articles for PubMed MeSH major topics NTSCI and NT-SCI, respectively, no articles were retrieved using the Major MeSH topics “spinal cord lesion” or “spinal cord lesions” with identical Entrez English language and date filters (**Table 1**). This low yield was unexpected and occurred even though the titles of 16 retrieved articles published between 1997 and 2002 contained the term “spinal cord lesion(s).”

The final aggregated dataset for our 3 primary outcome MeSH topic searches and 2 OVID search engines consisted of 126 original articles, of which 4 (3%) were systematic reviews (level 1A) and 2 (1.5%) were RCTs (level 1B) or controlled trials without randomization (ranked level 11A).

Research quality: Level 1-11A evidence

Due to the relatively few level 1-11A evidence articles retrieved and our exclusion of level 1V evidence, level 11B and 11I evidence accounted for a majority of the retrieved articles (**Figure 2**).

Four systematic reviews were retrieved; only 1 was retained for analysis after PRISMA statement ranking for evidence quality (**Table 2**). Of the excluded systematic reviews, 2 reported evidence in a prognostic domain (survival expressed as SMR and recovery),^{10,12} with key words encompassing demographics, survival, and rehabilitation outcomes. The Bransford et al paper¹² was excluded on the primary criteria of “SCI due to external causes incorrectly classified.” According to the PRISMA standard, this was ranked as a high-quality systematic review with 2 caveats: first, that fewer than 2 papers were related to NTSCI, and, second, that the 1 included paper involved

Figure 2. Article frequency (n) by evidence level 1A-11I.⁵ *11A-B prospective, **11B retrospective.

Table 2. Schekelle et al⁵ and PEDro article rankings (level 1A-11B)

Source	Setting	Domain	Cohort (n)	Evidence level (1-1V) ^a	Evidence statement (“”)
van den Berg et al, 2010 ¹¹	Systematic review	Prognostics	TSCI/NTSCI Studies (13)	1 (high)	“increased incidence in elderly likely due to non-traumatic SCI”
van den Berg et al, 2010 ^{10b}	Systematic review	Prognostics	TSCI/NTSCI Studies (16) TSCI (11) NTSCI (4) Both T/NTSCI (1) Cases (4,963)	1 (low)	“lower survival rates in non-traumatic c.f. traumatic and lower survival in traumatic than reference population”
McIntyre et al, 2014 ¹³	Systematic review	Intervention	TSCI/NTSCI/Other Studies (8) Cases (162)	1 (low)	“intrathecal baclofen is effective at reducing spasticity”
PEDro (Mean score/11)					
Esclarín-Ruz et al, 2014 ¹⁵	RCT	Intervention	TSCI/NTSCI Groups (4) Cases (88)	8	“Robotic-assisted step training effective in improving walking speed and LEMS”
Barry et al, 2013 ¹⁹	Pseudo-RCT; retrospective review with matched non-injured cohort	Prognostics	TSCI/NTSCI Groups (3) TSCI (6,672) NTSCI (3,566) Cases (10,238)	5.5	“NTSCI/D Veterans have a comparable prevalence of hypertension to those without SCI/D”
Scivoletto et al, 2003 ^{18b}	Pseudo-RCT (matched)	Prognostics	TSCI/NTSCI Groups (2) Cases (86)	5.5	“TSCI and NSCI patients had the same outcomes at discharge”
McKinley et al, 2001 ^{17b}	Pseudo-RCT (matched block)	Prognostics	TSCI/NTSCI Groups (2) Cases (176)	6	“Non-traumatic SCI shorter length of stay and lower overall functional improvement”

Note: LMNL = lower motor neuron lesion; NTSCI = nontraumatic spinal cord injury; RCT = randomized controlled trial; TSCI = traumatic spinal cord injury; UMNL = upper motor neuron lesion.

^aNTSCI: High, low, moderate ranking based on number of included studies. ^bIncluded studies: summative data extracted for analysis.

aortic aneurysm repair (AAR). The standardized taxonomy classifies iatrogenic cases such as AAR as traumatic, that is, the occurrence of traumatic SCI concomitant to surgical trauma (see ref. 1) in accordance with the definition of ICECI.³ The remainder of exclusions were made on the bases of statistical limitations ie, the authors’ decision to aggregate traumatic [T]SCI and NTSCI data for analysis thus precluding formal meta-analysis or less than 2 included papers were related to NTSCI.

Two systematic reviews previously had investigated aspects of NTSCI prognoses synthesizing incidence¹¹ and survival¹⁰ evidence obtained from 13 and 16 studies. Analysis of 13 critically appraised studies that investigated injury causation led these authors to conclude that there is good quality level 1A evidence for “increased incidence in elderly likely due to non-traumatic SCI”¹¹ (Tables 2 and 3). Regarding

survival, these authors found moderate-good level 1A evidence for “lower survival rates in non-traumatic compared with traumatic and lower survival in traumatic than reference population,” appraising 16 studies, 4 of which investigated non-traumatic patients.¹⁰ Of the excluded systematic reviews, McIntyre et al (2014) had retrieved 677 articles investigating intrathecal baclofen administration for intractable spasticity, including 8 non-RCT articles. Data pooling yielded a sample of 164 traumatic and non-traumatic patients. Modified Sackett level 1A evidence of poor quality was obtained, leading the authors to conclude that the evidence supporting the efficacy of intrathecal baclofen to reduce intractable spasticity in the first 6 months following injury may be subject to bias.¹³ The other excluded systematic review¹² examined thoracic SCI recovery and rehabilitation outcomes. The authors screened 486

Table 3. Summative data for level 1A-11B articles (n = 3; n = 4 citations)

Reference (n=3)	Citation (n=5)	Period	NTSCI population (causation)	Sample (N=5,588)	Outcome	Summative data (p value/ ratio)
van den Berg et al, 2010 ¹⁰	Ronen et al, 2004 ²⁷	1962-2000	All-cause	1,085	Median survival 24 yrs	
	Ronen et al, 2004 ²⁹	1962-2000	IVD herniation	158	Median survival 29 yrs	
	Ronen et al, 2005 ²⁸	1962-2000	Degenerative spinal stenosis	262	Median survival 17.6 yrs	
	Loblaw et al, 2003 ³⁰	1990-1995	Malignant SCC	3,305	Median survival 2.9 months	
Scivoletto et al, 2003 ¹⁸		1997-2001	All-cause	177	Higher odds onset age >50 yrs	<.001
			Inflammatory	40	No difference odds age >50 yrs	>.05
			Vascular	3	No difference odds age >50 yrs	>.05
			Neoplastic	39	No difference odds age >50 yrs	>.05
			Degenerative	62	No difference odds age >50 yrs	>.05
McKinley et al, 2001 ¹⁷		1992-1999	All-cause	87	Shorter rehabilitation LOS	<.000
				87	Lower FIM change	<.000
				87	Higher odds of institutionalization	4:1

Note: IVD = intervertebral disc; RR = relative risk; SCC = squamous cell carcinoma; FIM = Functional Independence Measure; LOS = length of stay.

articles and critically appraised 10, composed of 3 registries and 7 retrospective studies. Poor quality evidence, again subject to bias, was reported for all included studies (**Table 2**).

RCT level 1B evidence

Of the 4 original articles retrieved, consisting of 1 RCT and 3 matched block (nonrandomized) design pseudo-RCTs, 2 articles were retained to the analysis (**Table 2**). Included studies consisted of 2 matched block designs investigating relationships between etiology and rehabilitation outcomes¹⁷ and between age at injury and rehabilitation outcomes,¹⁸ respectively.

Of the excluded RCTs and pseudo-RCTs, gait training was examined in a sample of 88 traumatic and non-traumatic SCI subjects: 44 upper motor neuron lesion (UMNL), and 44 lower motor neuron lesion (LMNL) AIS C or D.¹⁵ The randomization strategy consisted of within-group random allocation to robotic or overground gait training, 22 per group (**Table 3**). A pseudo-RCT examined prevalence of hypertension in veterans (**Table 2**).¹⁹ A comparison of retrospective data obtained from the

medical records of TSCI patients (6,672), NTSCI patients (3,566), and 3,566 matched controls led these authors to conclude that “NTSCI/D Veterans have a comparable prevalence of hypertension to those without SCI/D.”

Evidence quality by research domain

Figure 3 presents results for the analysis of “nontraumatic” and “non-traumatic” articles ranked by Cochrane investigative domain. Of the 6 domains, 86 were prognostic (4.8% systematic reviews – level 1A), 14 interventions (14% RCT – level 1B), 8 diagnostic, 10 process of care, and 2 methodological. Qualitative methods were a major omission, with 1 exception – a thematic analysis of the lived experience.²⁰

Evidence quality by geographic region

Due to the influence of genetic diversity and environmental factors on systematic bias, retrieved articles were aggregated by geographic region. **Figure 4** presents the frequency and

Figure 3. Article frequency (n) by Cochrane domain.

Figure 4. Article frequency (n) by geographic region.

distribution of level 1-111 articles published 1997 to 2016 in relation to geographic region of origin. Authors from North America (Bransford et al¹²: paraplegia, rehabilitation outcomes; McIntyre et al¹³: spasticity); Europe (van den Berg et al^{10,11}: survival, incidence) were represented amongst the

systematic reviews (level 1A), whilst the geographic origins of the 4 level 1B/11A RCTs were Europe (2) and United States (2).

Figure 4 also shows the frequency of retrieved articles ranked level 11B or 111 and their distribution in relation to geographic region

of origin. Many investigators recruited cohorts from Europe (37), Northern America (29), and Australasia (17). Other retrieved articles reported the datasets of populations from the Middle East (5), the Subcontinent (6), Asia (4), and South America (1). Of the level 11B quasi-experimental studies and level 111 non-experimental descriptive studies, a defining feature was that a majority had aggregated non-traumatic and traumatic datasets for analysis. Whilst data aggregation improves statistical power, it concomitantly limits the relevance of a clinical dataset to EBM (Figure 5). Of the retrieved level 11B, or 111 articles, approximately 20% were categorized as observational (level 111) and only 5 reported the data of non-traumatic cases alone. The latter reports originated from Europe, North America, Australasia, and the Subcontinent.

Evidence quality and quantity by currency

Analysis by publication year revealed an increase in retrieval rate over a 2-decade period, with a 4-fold mean increase between 1997-2001 and

2012-2016 (Figure 6). Despite identification of a large level 11a/111 NTSCI literature (Figure 5) with apparent currency (Figure 6; means/SD per 5-year interval), all of the 3 summative reports listed in Table 3 were generated between 1996 and 2001. Regarding currency, these reports predated the publication of the consensus non-traumatic taxonomy.¹

Discussion

The term *non-traumatic SCI* describes a heterogeneous cluster of pathophysiological entities that broadly can be classified as relapsing/remitting and/or progressive or nonprogressive. Although significant advances continue to be made on the complex cytopathology of the various etiologies, experimental evidence for pathogenic cascades involving autophagy, apoptosis, necroptosis, neuroinflammation, dysmyelination, protein misfolding, and ubiquitinated inclusion bodies underscores a requirement for a medical evidence base to reduce uncertainty. Aside from commonalities in therapies targeted to sequelae

Figure 5. Subjects (cumulative *N*) enrolled in evidence level 1A-111 articles by etiology.

Figure 6. Article frequency (means/*SD*) by 5-year interval.

(intractable spasticity, neuropathic pain), a common denominator for many symptomatic patients is referral for medical rehabilitation in a specialist SCI treatment facility. This care continuum introduces levels of complexity regarding clinical decision making and health policy.²¹ Our mapping study evaluated the quality and quantity of the medical evidence base pertaining to NTSCI, as defined by the taxonomy of New and Marshall.¹ Mapping of 20-year data repository of “natural language patron terms” for “non-traumatic” SCI in the PubMed search engine was informative, showing that clinical judgment is a key component and pointing toward a knowledge gap that introduces uncertainty. A consistent finding was that low retrieval rates converged with both poor methodological quality and the currency of a limited high-quality literature to constrain formal evidence synthesis, as required for meta-analysis. The consequences are continued

reliance on expert opinion and clinical judgment, as well as overlap between medical rehabilitation and concurrent evidence synthesis and knowledge translation occurring in neurotrauma, oncology, and infectious disease.

Evidence for systematic bias

It is intuitively obvious that MeSH search English language filters introduce systematic bias toward articles that originate from better resourced regions, such as Europe and North America. Our mapping study revealed relationships between both the quality and quantity of NTSCI articles and geographic region of origin and these 2 variables and prognostic investigations. With the caveat that evidence derived from less resourced regions was under-represented in our database, referencing of the 3 level 1A systematic reviews retrieved from the United States and Europe

with the PRISMA statement checklist indicated that the methodological quality of each retrieved full-text study met the accepted EBM standard.² From this, we conclude that evidence of good quality shows that the occurrence of NTSCI is a functional correlate of advancing age¹¹ and, as such, the aging demographic of better resourced regions has implications for health policy. Notably, van den Berg et al reported that such cohorts have lower odds of survival, as measured using the SMR, when compared to their traumatic SCI counterparts and the reference population. These 2 factors, older age and NTSCI prevalence¹¹ and older age and survival,¹⁰ causally are interrelated by virtue of the linkage between loss of homeostasis at the cellular level, tissue damage, and intersection between chronic noninfectious diseases of aging and functional decline. Regarding rehabilitation outcomes, systematic reviews and case-controlled studies found population health evidence for relationships between non-traumatic etiology and length of stay and between etiology and functional improvement, although this was not a consistent finding.^{12,17,18} The findings of McKinley and coworkers¹⁷ indicated level 11B evidence for a “shorter length of stay, and lower overall functional improvement” for patients with all-cause NTSCI compared with their traumatic SCI counterparts. This relationship was found in a matched block comparison of traumatic SCI and NTSCI populations, allocated to 1 of 2 groups, powered for analysis at 88 patients per group. The Bransford et al¹² systematic review, which focused almost exclusively on traumatic SCI papers (specifically paraplegia), with just one included paper reporting non-traumatic cases, investigated the same rehabilitation outcome parameters. In contrast to McKinley et al,¹⁷ these authors found only “poor quality” evidence for a statistical relationship between thoracic injury and length of stay. Evidence for another important aspect of prognosis, neurological recovery, again was ranked as “poor quality.”¹² The results of our report were obtained after the exclusion of level V modified Sackett evidence (eg, case reports), which when interpreted in the light of prolific level 111 evidence, suggest that low quality evidence is formative in this context. Taken in conjunction with our finding of evidence bias toward better

resourced regions to the detriment of less resourced regions where many people are affected and issues of currency to consensus standards, these results may be important because they imply a need for a global approach to NTSCI to fill the evidence void.

Intervention

Our mapping study uncovered level 1A evidence for just one pharmacological intervention, which subsequently was excluded due to its statistical limitations (NTSCI and SCI datasets pooled for analysis). The consequences of this are, firstly, a limitation to the extent that this research evidence can inform patient-level decisions and, secondly, although populations of convenience satisfy ethical principles of equipoise, such strategies can introduce systematic bias. Both drug¹³ and device¹⁵ studies were underrepresented in our non-traumatic dataset, despite identification by Teasell et al²² in their systematic review that drug and medical device studies lend themselves to RCTs. Our results for pharmacological and medical device studies were not congruent with prolific RCT activity, as exemplified by the retrieval (2) and subsequent finding of 1 level 1B robotics study.¹⁵ (Notably, this low article retrieval rate was found despite that fact that exercise, gait training, and medication regimens are the mainstays of physical rehabilitation.) RCTs exclusively enrolling NTSCI patients are needed to determine when and how therapies should be applied in this context.

Systematic and other limitations

Of note for future directions, NTSCI is a relatively new descriptor and the articles retrieved from the “all-cause” NTSCI literature, as defined in the taxonomy of New and Marshall,¹ are constrained by the parsed terminology of the MeSH.²³⁻²⁵ Multidimensional mapping is beyond the scope of our investigator-led research program. However, it is acknowledged that a hierarchical and multi-axial mapping study would be necessary to thoroughly interrogate the taxonomy.

Bibliography, registry, and secondary searches were not conducted. This is an acknowledged limitation and may have introduced systematic bias. Another consideration for systematic bias

involves mapping of “key word” functions. Scoping searches conducted by our hospital librarian highlight the importance of consistency in selection of common rehabilitation terms and a need for an agreed key word terminology to optimize key word function searches.

Underrepresented investigative domains, such as methodology, diagnostics, and process of care, were a consistent finding. This led us to conclude that the quality and quantity of evidence in important domains is insufficient to draw meaningful conclusions about care or treatment guidelines. Aside from low article yield for pediatrics and qualitative methods, the emerging fields of health economics and large-scale genomics were notable omissions. This may reflect a limitation of our search strategy, which may have converged with the articles’ key words or the nature of the populations studied.

Analysis by geographic region identified systematic bias in our study, which was in part due to English language filters. Analysis of English language publications by geographic origin further suggests a role for publication bias within this very narrow EBM field towards better resourced countries; to fill this void, a global, multilingual approach may be necessary.

The 11-criteria PEDro scale ranked the methodological quality of RCTs.⁹ Macedo et al²⁶ demonstrated the face and construct validity of this instrument to rate the “methodological quality of RCTs in physiotherapy.” The authors’ validation process involved regressing PEDro scores against journal impact factors (convergent) and testing against 3 other scales (construct).²⁶ Notably, a PEDro score greater than 6 or less than 5 is an appropriate cut-off point for rating study quality. However, this tool was developed for use in ranking physiotherapy evidence, specifically the quality of RCTs.⁹ Its validity for ranking non-RCTs is topical. The PRISMA checklist was designed as a standard and is not a validated rating scale,⁷ although the authors allow for its use as a “gauge.”⁸ Recognizing that none of the available tools is ideal for ranking level 1 evidence, a major concern for future authors is that consistently low data yield together with limited standardized instruments may impact feasibility.

The decision to constrain search engines to 2 OVID databases was made in consultation with our research librarian. Restriction of the mapping protocol to one literature repository falls short of the PRISMA standard.⁷ Although standardized searches performed across multiple search engines and bibliography searches are recommended,⁸ EMBASE was rejected on the grounds that it is a European-centred repository; PsycINFO (OVID) and CINAHL are psychology and nursing repositories, respectively. Exhaustive bibliography searches also were rejected based upon dataset currency. In agreement with New and Delafosse,¹⁴ the clinical terms “non-traumatic” and “nontraumatic” are synonyms. However, our experience shows that the MeSH terms are not interchangeable in search engine vocabularies. Of relevance to these observations,¹⁴ Gault et al²³ offer a cogent explanation involving the parsing of the medical vocabulary. Thus precautions, such as consulting a research librarian, may be necessary when mapping generic terms.^{24,25}

Future directions

EBM is grounded in population health principles²; as such, it is notable that 3 of the 4 systematic reviews identified satisfied the PRISMA conduct and reporting standard⁶⁻⁸ (Tables 3 and 4). However, our systematic review has shown that the mapping of non-traumatic SCI datasets is not straightforward. Other descriptive terms may be utilized in the future.¹⁴ The assembly of a large expert consortium resourced for multidimensional mapping may be a logical next step.

Despite a large prognostic literature, it is necessary to continue to advance our knowledge about other investigative domains and how these might guide practice. Of these diagnostics, intervention and process of care are key investigative areas; clearly there is more to learn regarding genetics, paediatrics, and knowledge translation.⁴

Conclusion

Mapping studies continue to advance knowledge about the medical evidence base underpinning knowledge translation in traumatic SCI. Our

mapping study suggests that there will be evidence gaps for non-traumatic patients, primarily because of the nature of the available data and its limited capacity to support knowledge translation. Our findings underscore the need for qualitative and quantitative research on the occurrence of non-traumatic SCI in all contexts, especially in less resourced settings.

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Appendix A

Search Strategy with MeSH Terms and Filters

1. PubMed nontraumatic spinal cord injury/
date/English language filter
2. PubMed nontraumatic spinal cord injury/
date/ English language filter/review
3. PubMed nontraumatic spinal cord injury/
date/English language filter/case report
4. PubMed non-traumatic spinal cord injury/
date/English language filter
5. PubMed non-traumatic spinal cord injury/
date/English language filter/review
6. PubMed non-traumatic spinal cord injury/
date/English language filter/case report
7. PubMed non traumatic spinal cord injury/
date/English language filter
8. PubMed spinal cord lesion/date/English
language filter
9. PubMed spinal cord lesions/date/English
language filter
10. PubMed spinal cord disease/date/English
language filter
11. PubMed spinal cord injury not due to
trauma/date/English language filter
12. MEDLINE nontraumatic spinal cord injury/
date/English language filters*
13. MEDLINE non-traumatic spinal cord injury/
date/English language filters*
14. MEDLINE nontraumatic spinal cord injury/
date/English language filters/key word*
15. MEDLINE non-traumatic spinal cord injury/
date/English language filters/key word*